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Agenesis of the Corpus Callosum in a Mother and Son

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Most reported familial cases of agenesis of the corpus callosum have followed either an autosomal recessive or an X-linked recessive pattern of inheritance. To the best of our knowledge, there is only one previous report of a family showing clear-cut autosomal dominant inheritance. We present the second such family, among whom a mother and her son had moderately severe coordination problems and low-normal intelligence. We suggest that agenesis of the corpus callosum, when transmitted as an autosomal dominant trait, is clinically characterized by a relatively milder phenotype than that occurring when inheritance is either autosomal or X-linked recessive and may be more common than has been thought. Am. J. Med. Genet. 69:152–154, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: agenesis of corpus callosum; autosomal dominant inheritance; poor coordination

INTRODUCTION

Agenesis of the corpus callosum is usually a sporadic trait, but sometimes it occurs in families. There are several reports of probable autosomal recessive or X-linked recessive inheritance [Cao et al., 1977; Dogan et al., 1967; Kaplan, 1983; Lachiewicz et al., 1985; Luef et al., 1992; Menkes et al., 1964; Naiman and Fraser, 1955; Pineda et al., 1984; Shapira and Cohen, 1973; Vles et al., 1993; Wilson et al., 1983; Young et al., 1985; Ziegler, 1958]. To the best of our knowledge, however, there is only one previous report of a family showing clear autosomal dominant inheritance [Lynn et al., 1980]; we report herein on a second family showing this mode of inheritance.

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CLINICAL REPORTS

Patient 1

The propositus was the product of a normal term pregnancy and delivery, with a birth weight of 2,800 g. His motor development was delayed. He started walking independently at 2 years of age, only after 6 months of physiotherapy and occupational therapy, and began speaking single words at 2 years of age. His medical history was otherwise unremarkable. He was referred to the Child Development Unit at the age of 7 years for assessment of marked hyperactivity, learning disabilities, impulsive behavior, and short attention span. At the time, he was a first-grade pupil in the remedial class at a normal school.

Physical examination showed a normal child with no minor anomalies. Height and weight were each at the 10th centile, and head circumference was at the 40th centile. Neurological status was normal, but he demonstrated clumsiness, mainly in fine motor skills. His general behavior was immature, his attention span was short, and he had specific learning problems. He also had occasional nocturnal enuresis. He was diagnosed with attention deficit hyperactivity disorder (ADHD) and learning problems and began treatment with methylphenidate in combination with psychotherapy.

Neuropsychological testing demonstrated low performance in cognitive tests, especially for those tasks that rely on right hemispheric function. Visuomotor coordination skills, such as handwriting, drawing, and copying pictures, were poor. He had problems with interpersonal communication, limited understanding of humor, and poorly defined limits of behavior. Full-scale IQ was 82.

Laboratory investigations all showed normal results. These included biochemical profile (specifically for thyroid function, renal function, and liver function), full blood count, and muscle creatine phosphokinase. Urine chromatography for amino acids and sugars was normal. Fragile-X DNA testing performed on both the mother and the son gave normal results.

Cranial CT scan showed agenesis of the corpus callosum. At this time, he was also complaining of visual problems and was therefore prescribed glasses, without improvement. Visual evoked potentials showed abnor-

mal functioning of the optic nerves. MRI of the skull (Fig. 1) confirmed agenesis of the corpus callosum, with a colpocephalic dilatation of the lateral ventricles.

The patient's behavior and attention span at school improved with continued use of methylphenidate and psychotherapy. At the time of his last visit to the unit 2 years later, his behavior had improved to the point where he was functioning academically at an average level, in a special setting in which learning-disabled children are integrated into a class of normal children, but his social functioning remained poor.

Patient 2

The mother was 35 years old and at the time was a housewife. She had worked in a factory, sewing on buttons, but was incapable of managing this task due to problems caused by poor coordination. As a result, it was recommended that she be referred for medical investigation of her poor visual and motor coordination. She then underwent a CT scan of the skull, which showed absence of the corpus callosum. An MRI of the skull (Fig. 2) showed findings identical with those in her son.

Neuropsychological assessment showed her to be functioning at a level rather lower than that of her son. Her ability to write, draw, and copy pictures was very poor. She was completely incapable of managing money and succeeded in coping at home only with the constant help and support of her sisters. Full-scale IQ was 66. Chromosome analysis showed a normal female karyotype.

Fig. 1. Cranial MRI scan of the son.

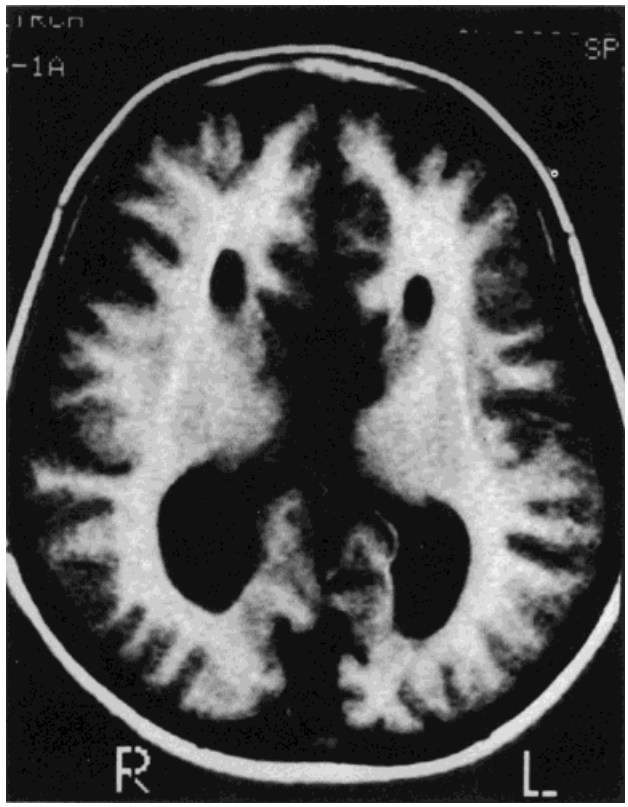

Fig. 2. Cranial MRI scan of the mother.

Family History

The parents were not consanguineous. The father was a 36-year-old technician in good general health. Cranial CT scan performed on the father was normal. The propositus has an older sister who is completely normal. Cranial CT scans were also performed on the mother's parents. Both were normal, suggesting that her agenesis of the corpus callosum arose as a result of a new mutation.

DISCUSSION

In most of the previously reported cases of agenesis of the corpus callosum, in which the mode of inheritance is either autosomal or X-linked recessive, those affected had psychomotor retardation ranging from moderate to severe [Cao et al., 1977; Dogan et al., 1967; Kaplan, 1983; Lachiewicz et al., 1985; Luef et al., 1992; Menkes et al., 1964; Naiman and Fraser, 1955; Pineda et al., 1984; Shapira and Cohen, 1973; Vles et al., 1993; Wilson et al., 1983; Young et al., 1985; Ziegler, 1958]. In contrast, in the family we describe, the son had low-normal intelligence and the mother was mildly retarded, and both had poor coordination.

We have found only one other report describing a family with clear-cut autosomal dominant inheritance [Lynn et al., 1980]; a father and son were both shown on CT scan to have complete agenesis of the corpus callosum, with associated abnormalities of the ventricles. The son had learning disabilities, poor coordination,

and megalencephaly but was otherwise normal. The father had megalencephaly but no other signs and reported that his mother had also had a large head. Interestingly, of all the previously described cases, those who most closely resemble ours clinically are the father and son described in the report of Lynn et al. [1980].

Inheritance in the present family confirms the existence of an autosomal dominant form of agenesis of the corpus callosum, in which the phenotype is milder than that occurring when the mode of inheritance is the more common autosomal or X-linked recessive type. Even the mother, who was more severely affected than the child, managed to function in her day-to-day life, albeit with help from her family, was married, and had children. The fact that she remained undiagnosed for many years indicates that this condition may be underdiagnosed. This should be borne in mind in evaluating familial poor coordination, and a cranial CT scan should be performed. The similarities, both in the mode of transmission and in the clinical picture, between the patients described by Lynn et al. [1980] and our family lead us to speculate that the causative genetic or molecular defect might be the same.

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